

Prostatic Diseases and Male Voiding Dysfunction

Correlation of Ultrasonically Determined Bladder Wall Thickness and Prostatic Calcification With the Urinary, Psychosocial Dysfunction, Organ Specific, Infection and Neurological/Systemic Symptoms, and Tenderness Scoring System



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OBJECTIVE	To evaluate ultrasonically determined bladder wall thickness (BWT) and prostatic calcification presence, in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and to correlate the findings with patient characteristics and the urinary, psychosocial dysfunction, organ specific, infection and neurological/systemic symptoms, and tenderness (UPOINT) classification system.
MATERIAL AND METHODS	Between January 2008 and December 2017, data of 1294 patients diagnosed with chronic prostatitis, in a single urology clinic, meeting a number of selective inclusion/exclusion criteria, were retrospectively analyzed. Patients, compliant to fill out all requested questionnaires, between the ages of 21-65 years were included to the study. Exclusion criteria were noncompliance of filling out required questionnaires, acute and/or chronic bacterial prostatitis, history of genitourinary cancer, history of recent prostate surgery, and diagnosis of neurological diseases affecting the bladder.
RESULTS	The median patient age and UPOINT subdomain was determined as 37 (IQR = 13, range 21-65) and 2 (IQR = 1, range 0-5), respectively. Median values for BWT, National Institute of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), and International Index of Erectile Function were 3 (IQR = 1, range 2-6, 7), 4 (IQR = 6, range 1-23), and 25 (IQR = 10, range 1-30), respectively. The presence of calcification demonstrated a significant association with total NIH-CPSI score and BWT, whereas its relation with age and total UPOINT score was insignificant. However in contrast to calcification status, BWT ≥ 3.3 showed a strong and statistically significant relation to all the described measurements.
CONCLUSION	Measurement of BWT can be used as an accessible and objective method for the diagnose of CP/CPPS according to UPOINT scoring system. UROLOGY 124: 218–222, 2019. © 2018 Elsevier Inc.

Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is a common condition that significantly impacts quality of life, but its etiology is

poorly understood.¹ Because of the clinical diversity of CP/CPPS patients, it has been suggested that patients should be classified into a unique clinical phenotype, individually.

For this reason a new classification (scoring) system based on 6 symptom categories, called UPOINT, that initializes urinary, psychosocial dysfunction, organ specific, infection and neurological/systemic symptoms, and tenderness of the pelvic floor, has been currently validated by several studies.²⁻¹² It was shown that the severity and interval of prostatitis symptoms according to the National

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Institute of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) were in correlation with the number of positive UPOINT domains.⁸

Previously conducted studies demonstrated that the Urinary subdomain is the most frequently appearing subgroup in the UPOINT scoring system, which was mostly evaluated according to patient records and/or postvoid residual urine (PVU >100 mL). However, during the examination of infravesical obstruction, a thickened or trabeculated bladder wall is acknowledged as an important sign indicating obstruction. Despite some contradictory results of ultrasonically determined bladder wall thickness (BWT) measurements, great attention in its clinical benefit is still in progress.¹³⁻¹⁵

It is assumed that prostatic calcifications, which are seen very commonly, derive by precipitations structured through an ongoing inflammation that affects prostatic secretory materials and calcifications of the corpora amygdacea.¹⁶ Furthermore, extension of symptomatic periods and major intraprostatic inflammation or microbial settlement are suggested to correlate with the presence of prostatic calcifications in CP/CPSP patients.^{17,18}

With respect to this, we wished to evaluate ultrasonically determined BWT and the presence of prostatic calcification, in a community of men with CP/CPSP, and correlate the findings with patient characteristics and the UPOINT classification system.

METHODS

The present study was performed on patients who were subjected to diagnostic and therapeutic protocols routinely adopted in our clinical practice. Patients provided written informed consent to anonymous publication of their clinical data.

Between January 2008 and December 2017, the clinical data of 1294 patients, diagnosed with chronic prostatitis in a single urology outpatient center, meeting a number of selective inclusion/exclusion criteria, were retrospectively analyzed.

Medical history collection as well as clinical and microbiological diagnosis of patients have been described particularly in a previous report of the present study,¹⁰ focusing on the diagnosis and UPOINT phenotyping of CP/CPSP patients.

Patients who were compliant to fill out all questionnaires between the ages of 21-65 years were included to the study. Besides, in addition to the originally described inclusion criteria of the urinary subdomain, like CPSI urinary score >4, patient complaint of bothersome urgency, frequency, or nocturia and/or PVU volume >100 mL, BWT measurement and the presence of prostatic calcification during pelvic ultrasound imaging were assessed in all patients for adjunct correlation. Exclusion criteria were determined as noncompliance of filling out required questionnaires, acute and/or chronic bacterial prostatitis, history of genitourinary cancer, history of recent prostate surgery, and diagnosis of neurological diseases affecting the bladder.

Patients were separated into 3 domains as severe dysfunction (>29), moderate dysfunction (16-29), and mild dysfunction (0-15) according to their symptom degrees on the NIH-CPSI score. At least 1 UPOINT subdomain positivity was present in all patients. The presence and severity of erectile dysfunction (ED) in patients were determined using the International Index of

Erectile Function (IIEF) survey form in 5 classes as follows: no dysfunction (25-30 points), mild dysfunction (19-24 points), mild to moderate dysfunction (13-18 points), moderate dysfunction (7-12 points), and severe dysfunction (0-6 points), respectively.

Statistical Evaluation

Data were analyzed using the R statistics program. All the continuous variables were tested for normality using Shapiro-Wilks test, PP, and QQ plots. The quantitative variables were found to be non-normally distributed, therefore they were summarized by median, interquartile range (IQR), minimum, and maximum values. The qualitative variables were summarized by frequencies and percentages. The correlations were calculated using Kendall's tau b correlation due to high number of tied observations and the 95% bootstrap confidence intervals using "kendall.ci" function in "NSM3" package were provided. It was of interest to test whether calcification had an effect on UPOINT score. Somer's D measure of directional association was calculated between the ordinal UPOINT score and calcification status, taking the UPOINT score as a dependent variable.

Age, BWT, IIEF, NIH-CPSI, and total UPOINT score were compared between calcification status and BWT groups using Mann-Whitney *U* test. A value of $P < .05$ was considered statistically significant. Other than marginal tests which compared the groups with respect to a single variable, ordered logistic regression model was fit to see whether BWT, calcification status (+/-), age, inflammatory status (+/-), NIH-CPSI, or IIEF has effect on UPOINT controlling (adjusting) for other variables. UPOINT was divided into 3 ordinal classes such that 1-2, 3, and 4-5 constructed the 3 classes and was used as a dependent variable in the ordered logistic regression model. The Bonferroni correction was applied to the significance level correlation test, thus a P value of .007 was considered significant. In other cases, a value of $P < .05$ was considered statistically significant.

RESULTS

A total of 87 acute and/or chronic bacterial prostatitis patients (incl., 12 noncompliant patient in filling out all questionnaires), 8 patients with a history of genitourinary cancer (incl., 1 noncompliant patient in filling out all questionnaires), 23 patients with a history of recent prostate surgery (incl., 2 noncompliant patient in filling out all questionnaires), and 4 patients with a diagnosis of neurological diseases affecting the bladder were excluded. In addition 206 noncompliant CP/CPSP patients, with missing 1 or more required inquiry results were determined by scanning the clinical database and excluded.

Consequently, descriptive statistics and clinical characteristics of 966 CP/CPSP patients meeting the study criteria, are summarized in Table 1. The subjects in this study were a mixture of 521 newly diagnosed, relatively treatment naive (usually antibiotics or anti-inflammatory agents), 369 recurrent patients, and 79 tertiary referral patients, in whom multiple previous therapies had failed.

The median patient age was calculated as 37 (IQR = 13, range 21-65) and the median UPOINT subdomain number was determined as 2 (IQR = 1, range 0-5). Median values for BWT, NIH-CPSI, and IIEF were 3 (IQR = 1, range 2-6, 7), 4 (IQR = 6, range 1-23), and 25 (IQR = 10, range 1-30), respectively.

Age, BWT, and IIEF score correlations with the UPOINT classification system were found to be irrelevant, whereas its correlation with NIH-CPSI and the correlation of NIH-CPSI with BWT showed statistically significant results.

Table 1. Descriptive statistics for patient characteristics and subdomain scores

Variables	Median	IQR	Min.	Max.
Age (y)	37	13	21	65
BWT (mm)	3	1	2	6.7
NIH-CPSI (<i>n</i> = 966, %)	10	10	3	34
Mild—(838, 86%)				
Moderate—(123, 13%)				
Severe—(5, 1%)				
IIEF (<i>n</i> = 966, %)	25	10	1	30
No ED—(498, 52%)				
Mild—(305, 31%)				
Mild to moderate—(122, 13%)				
Moderate—(33, 3%)				
Severe—(8, 1%)				
UPOINT (<i>n</i> = 966, %)	2	1	1	5
Urinary—(569, 59%)				
Psychosocial—(503, 52%)				
Organ specific—(354, 36%)				
Infections—(163, 17%)				
Neurological systemic—(205, 21%)				
Tenderness—(387, 40%)				

BWT, bladder wall thickness; IIEF, International Index of Erectile Function; IQR, interquartile range; NIH-CPSI, National Institute of Health-Chronic Prostatitis Symptom Index; Max., Maximum; Min., Minimum.

The associations between BWT and urinary, organ specific, and skeletal muscle tenderness subdomains were found statistically significant with *P* values of <.001, <.001, and .002 respectively. Urinary and organ specific rates were higher in patients with a BWT ≥ 3.3 mm (44.6 vs 55.4 and 48% vs 52% respectively). On the other hand, skeletal muscle tenderness rate was higher in patients with a BWT <3.3 mm (61.8% vs 38.2%).

Somer's D measure of association between the UPOINT allocation and calcification status were calculated as 0.064 (95% confidence intervals: -0.012, 0.146) taking UPOINT as a dependent variable. The association was weak and not significant (*P* = .103). The associations between calcification and each UPOINT subdomain was found insignificant, with *P* values of .834, .783, .099, .197, .129, and .282 respectively.

The comparisons of patients' characteristics and scores with respect to BWT or calcification status are shown in Tables 2 and 3. The presence of calcification demonstrated a significant association with total NIH-CPSI score and BWT, whereas its relation with age and total UPOINT score was insignificant. However, in

contrast to the calcification status, BWT ≥ 3.3 mm showed a strong and statistically significant relation with all the described parameters.

Ordered logistic regression results were given in Table 4. Comparisons were carried out at each possible cutoff along the ordinal scale (2 for 3-level ordinal outcome variable, UPOINT-3). The model satisfied the proportional odds assumption due to likelihood ratio test in VGAM package, thus it was assumed that in each of the comparison, the odds ratio assessing the effect of an exposure variable was the same. This model was fit using the training data which constructed 70% of the whole data set and the rest of the data was used for testing the model. The model accuracy using the test data was 68% which was acceptable and also the deviance was tested and the model seemed to be a good fit.

According to the results given in Table 4, BWT and inflammatory status were statistically significant at 0.05 significance level. For a 1 unit increase in BWT, we expect a 0.187 increase in the ordered log odds of being in a higher level of UPOINT, given all other variables are held constant (OR = 1.206, *P* = .042). The patients with inflammation compared to the patients without inflammation was at 1.406 times higher odds of having a higher UPOINT score at either 1 of the 2 thresholds adjusting for BWT, calcification, and age (*P* = .036).

DISCUSSION

The major findings of the present study are as follows: (1) BWT ≥ 3.3 mm demonstrated strong and significant associations with age, IIEF, total UPOINT, and NIH-CPSI scores of CP/CPPS patients, (2) despite its statistically significant relation with BWT, total NIH-CPSI, and IIEF scores, the influence of calcification status on UPOINT scoring was found insignificant, and (3) no correlation between ED and the UPOINT classification system was determined, as in our previously accomplished study.¹⁰

To our knowledge this is the first study evaluating the association and impact of BWT measurement and/or prostatic calcification status to the newly described UPOINT system.

The urinary subdomain of UPOINT was defined as CPSI urinary score >4, patient complaint of bothersome urgency, frequency, or nocturia and/or PVU volume >100 mL.⁸ It is known that, commonly in non-neurologically affected patients, detrusor underactivity, bladder outlet obstruction, or dysfunctional voiding are the main

Table 2. Comparisons of patient characteristics and scores with respect to calcification status

Variables	Calcification				<i>P</i> Value [†]
	No (<i>n</i> = 658)		Yes (<i>n</i> = 308)		
	Median (IQR)	Range	Median (IQR)	Range	
Age	37 (13)	21-65	38 (13)	21-57	.578
Total NIH-CPSI	7 (6)	3-31	8 (6)	3-34	.002*
BWT	3 (1)	2.4-6.7	3.3 (1.08)	2.3-6.7	.031*
IIEF	25 (9)	1-30	23 (9)	5-30	<.001*
Total UPOINT	2 (1)	1-5	2 (1)	1-5	.091

[†] Mann-Whitney *U* test *P* value.

Table 3. Comparisons of patient characteristics and scores with respect to BWT groups

Variables	BWT (mm)				P Value [†]
	<3.3 mm (n = 538)		≥3.3 mm (n = 428)		
	Median (IQR)	Range	Median (IQR)	Range	
Age	36 (10)	21–56	39 (11)	21–65	<.001*
Total NIH-CPSI	6 (4)	3–21	11 (8)	3–34	<.001*
IIEF	26 (9)	5–30	23 (10)	5–30	<.001*
Total UPOINT	2 (1)	1–5	2 (1)	1–5	<.001*

[†] Mann-Whitney U test P value.

Table 4. Ordered logistic regression of UPOINT (3 classes) on BWT, calcification, age, and inflammatory status

Variables	Estimate	Std. Error	Z Value	P Value	QR
Intercept 1 (UPOINT = 1 or 2 (ref.) vs 3 and 4 or 5)	−0.720	0.664	−1.084	.278	0.487
Intercept 2 (UPOINT = 1 or 2 and 3 (ref.) vs 4 or 5)	−2.343	0.672	−3.488	.004	0.096
Calcification (+)	0.288	0.171	1.687	.091	1.334
BWT	0.187	0.092	2.036	.042*	1.206
Age	0.006	0.011	0.546	.585	1.006
Inflammatory status (+)	0.341	0.163	2.097	.036*	1.406

reasons causing lower urinary tract symptoms (LUTS) and/or high PVU. Furthermore, untreated infravesical obstructions can persist normal bladder function for an extended duration of time, even though bladder detrusor hypertrophy occurs.

Thus, several studies investigated the clinical utility of BWT measurements predicting LUTS, especially in benign prostatic hyperplasia.^{13-15,19-23} Commonly it was concluded that, even urodynamic investigation still remains the gold standard for bladder outlet obstruction diagnosis, measurement of BWT is an effective method anticipating LUTS. The urinary subdomain, which is interrogated and seen most frequently in both the NIH-CPSI and UPOINT scoring systems, is mainly detected according to subjective complaints of the patient. We believe that these subjective definitions did not gain any diagnostic benefit to the already existing complex nature of CP/CPPS and the applied classifications. Therefore, our intention was to contribute to use this simple and noninvasive method as an objective criteria for the urinary subdomain and to evaluate its relation with the UPOINT grading system.

According to the study of Hakenberg et al, we showed that BWT ≥3.3 mm had a positive and statistically significant association with the total NIH-CPSI score, the total UPOINT score, and the urinary subdomain.²⁴

In addition to those, recently there has been a great interest investigating the relationship between LUTS or CP/CPPS and prostatic calcifications demonstrating positive correlation.

Shoskes et al¹⁷ investigated the prevalence of prostatic calcifications in 130 men with CP/CPPS and claimed that no association with the total NIH-CPSI score exists, which was not supported by our results. Nevertheless, due to their major impact, differences between the method of ultrasonic measurement (transrectal vs abdominal), age,

and size of the study population were considered as the main reasons for this disagreement.

The study performed by Zhao et al¹⁶ under 358 CP/CPPS patients, pointed out that the presence of calcification had a statistically significant impact on ED which was in agreement with our findings. However, they reported that in CP/CPPS type 3A patients the presence whereas in CP/CPPS type 3 B patients the absence of calcification was statistically significant, which was not supported by our results. This discrepancy was thought to appear due to the relatively great difference among the ages of both study population, as it is presumed that prostatic calcifications are commonly seen in older men.²⁵

Additionally, in the study by Kim et al²⁶ reviewing pathologic specimens of 225 patients who underwent transurethral prostate resection, reported no relation between prostatic inflammation and prostatic calculi related to our findings.

Geramoutsos et al²⁷ investigated the incidence, morphology, and clinical presentations of prostatic calculi in 101 men diagnosed with CP/CPPS, stated that the presence of calculi was correlated with advanced age (>40 years) and it was claimed that the presence of symptoms are positively correlated with the size of prostatic calculi. Because we did not categorize our patients according to their size of calculi, this suggestion could not be interpreted literally. But nevertheless, in contrast to our used UPOINT grading system that showed no statistically significant relation, the lack of a validated symptom score was thought to indicate their conclusion debatable.

Some limitations of the present study have to be considered. First, even we evaluated a large patient population, the retrospective nature, and the absence of a healthy control group, which could raise some interpretational diversity. However, none of the previously performed studies investigating prostatic calcification defined

a healthy control group. Second, describing prostatic calcifications by the utilization of transrectal ultrasonography more specifically, rather than present or absent, could reveal more data on its clinical importance. Further studies in this regard have to be achieved.

In conclusion, measurement of BWT can be used as an accessible and objective method for the diagnose of CP/CPPS according to UPOINT scoring system, whereas the impact of prostatic presence was found insignificant.

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